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| EXAMINER | |
|---|---|
| ZHENG, LI | |
| **ART UNIT** | **PAPER NUMBER** |
| 1638 | |

DATE MAILED: 08/23/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/615,005 | WRIGHT ET AL. | |
| | Examiner | Art Unit | |
| | Li Zheng | 1638 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *29 October 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *49* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *49* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

### *Specification*

1. The disclosure is objected to because of the following informalities:

The paragraph beginning Page 1, line 7 recites U.S. Patent application 09/965,553. The status of this application should be indicated.

Appropriate correction is required.

2. The specification is objected under 37 CFR 1.821(d) as failing to refer to the sequence by use of the sequence identifier, preceded by "SEQ ID NO:" in the text of the sequences listed on page 43, 45 and 53-56.

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claim 49 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 49: the recitation, "a seventh nucleotide sequence comprising SEQ ID NO: 4", renders the claim indefinite, because SEQ ID NO: 4 is a protein sequence. The metes and bounds are unclear.

4. Claim 49 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

A review of the full content of the specification indicates that obtaining nucleotide sequences that are at least about 95% identical to SEQ ID NO: 2 or nucleotide sequences that are at least about 70% identical to SEQ ID NO: 9, or nucleotide sequences encoding polypeptides having at least 75% identity to SEQ ID NO: 10 or nucleotide sequences that are at least about 70% identical to SEQ ID NO: 11, or nucleotide sequences encoding polypeptides having at least 79% identity to SEQ ID NO: 12, or nucleotide sequences that are at least about 70% identical to SEQ ID NO: 15, or nucleotide sequences encoding polypeptides having at least 90% identity to SEQ ID NO: 16, or nucleotide sequences that are at least about 50% identical to SEQ ID NO: 5, or nucleotide sequences encoding polypeptides having at least 30% identity to SEQ ID NO: 6 is essential to the operation of the claimed invention. A review of the full content of the specification also indicates that the right organization of the structure is important to distinguish Cyclops retrotransposon from other types of transposon.

The Federal Circuit has recently clarified the application of the written description requirement. The court stated that a written description of an invention "requires a precise definition, such as by structure, formula, [or] chemical name, of the claimed subject matter sufficient to distinguish it from other materials." (See *University of California v. Eli Lilly and Co.*, 119 F.3d 1559, 1568; 43 USPQ2d 1398, 1406 (Fed. Cir. 1997)). The court also concluded that "naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material." Id. Further, the court held that to adequately describe a claimed genus, Patent Owner must describe a representative number of the species of the claimed genus, and that one of skill in the art should be able to "visualize or recognize the identity of the members of the genus." Id.

A review of the language of claim 49 indicates that the claim is broadly drawn to genera of nucleotide sequences that are at least about 95% identical to SEQ ID NO: 2 or nucleotide sequences that are at least about 70% identical to SEQ ID NO: 9, or nucleotide sequences encoding polypeptides having at least 75% identity to SEQ ID NO: 10 or nucleotide sequences that are at least about 70% identical to SEQ ID NO: 11, or nucleotide sequences encoding polypeptides having at least 79% identity to SEQ ID NO: 12, or nucleotide sequences that are at least about 70% identical to SEQ ID NO: 15, or nucleotide sequences encoding polypeptides having at least 90% identity to SEQ ID NO: 16, or nucleotide sequences that are at least about 50% identical to SEQ ID NO: 5, or nucleotide sequences encoding polypeptides having at least 30% identity to SEQ ID NO: 6. A review of the language of claim 49 also indicates that the claim is drawn to

nucleotide sequences that have two PBS sites at 5' end and have an integrase domain (a third nucleotide sequence) located upstream of a reverse transcriptase domain (a fourth nucleotide sequence).

The specification indicates that the Calypso-1, -2, and –3 retrovirus-like elements were aligned using the Clustal X v1.63b program to generate a consensus sequence. The amino acid sequence encoded by the consensus sequence was determined and compared to amino acid sequences of retrovirus-like element from soybean, pea, and Athila-like elements of Arabidopsis. A new consensus sequence was determined from the coding regions of the protease, reverse transcriptase, and integrase (pages 56-57, Example 4). A summary of the sequence listing on pages 19-20 indicates that SEQ ID NO: 1 and 2 are specialized primer binding site version 1 and 2, respectively, and that SEQ ID NO: 9 encodes SEQ ID NO: 10 which is generic integrase; SEQ ID NO: 11 encodes SEQ ID NO: 12 which is generic reverse transcriptase; SEQ ID NO: 15 encodes SEQ ID NO: 16 which is generic RNAseH; SEQ ID NO: 5 encodes SEQ ID NO: 6 which is generic envelope; and SEQ ID NO: 3 and 4 are specialized polypurine tract and targeting sequence, respectively.

However, the specification does not describe conserved structures of SEQ ID NO: 2, 9-12, 15, 16, 5, and 6 that are essential for their functions. For example, the specification does not describe any nucleotide sequences that have at least 70 identity with SEQ ID NO: 11, or which encode amino acid sequence having at least 79% identity to SEQ ID NO: 12. The specification does not teach the changes that can be made to SEQ ID NO: 11 or 12, such that nucleotide sequences that differ from SEQ ID NO: 11

by as much as 30% and amino acid sequences that differ from SEQ ID NO: 12 by as much as 21%, still retain their functional properties. Same argument holds for SEQ ID NO: 2, 9, 10, 15, 16, 5, and 6 as well. See Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 18 USPQ 2d 1016 at 1021 and 1027, (Fed. Cir. 1991) at page 1021, where it is taught that a gene is not obtained until the inventor can define it by "its physical or chemical properties" (e.g. a DNA sequence). Also see *University of California v. Eli Lilly and Co.*, 119 F.3d 1559, 1568; 43 USPQ 2d 1398, 1406 (Fed. Cir. 1997), where it states: "The name of cDNA is not in itself a written description of that DNA; it conveys no distinguishing information concerning its identity. While the example provides a process for obtaining human insulin-encoding cDNA, there is no further information in the patent pertaining to that cDNA's relevant structural or physical characteristics; in other words, it thus does not describe human insulin cDNA ...Accordingly, the specification does not provide a written description of the invention...". Also see Fiers v. Revel 25 USPQ 2d (CAFC 1993) at 1606, which states that "[a]n adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself".

Further, the specification does not describe two copies of primer binding site (PBS) next to the left LTR region as first and second nucleotide sequences in claim 49. It does not correlate such structure to the function. The only structure described in specification regarding PBS site is only one copy of either first or second nucleotide

sequence. Still further, the specification does not describe an integrase domain of SEQ ID NO: 10 upstream to a reverse transcriptase domain of SEQ ID NO: 12. The specification only describes a retrotransposon with an integrase domain located after RNAseH domain of SEQ ID NO: 16. Finally, the claim does not describe other essential parts of the retrotransposon such as gag and LTR regions, neither does it imply that the claimed nucleotide sequence should contain those elements. Therefore, given the breadth of the claims and the lack of further guidance, a person skilled in the art would conclude that applicant is not in possession of the claimed invention.

5. Claim 49 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for SEQ ID NO: 1-3,5-6,9-12,15 and16 does not reasonably provide enablement for nucleotide sequences that are at least about 95% identical to SEQ ID NO: 2 or nucleotide sequences that are at least about 70% identical to SEQ ID NO: 9, or nucleotide sequences encoding polypeptides having at least 75% identity to SEQ ID NO: 10 or nucleotide sequences that are at least about 70% identical to SEQ ID NO: 11, or nucleotide sequences encoding polypeptides having at least 79% identity to SEQ ID NO: 12, or nucleotide sequences that are at least about 70% identical to SEQ ID NO: 15, or nucleotide sequences encoding polypeptides having at least 90% identity to SEQ ID NO: 16, or nucleotide sequences that are at least about 50% identical to SEQ ID NO: 5, or nucleotide sequences encoding polypeptides having at least 30% identity to SEQ ID NO: 6, or the isolated nucleotide sequence that containing only PBS, integrase, reverse transcriptase, RNAseH, envelope, and target site. The specification

does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make/use the invention commensurate in scope with these claims.

The specification indicates that the Calypso-1, -2, and –3 retrovirus-like elements were aligned using the Clustal X v1.63b program to generate a consensus sequence. The amino acid sequence encoded by the consensus sequence was determined and compared to amino acid sequences of retrovirus-like element from soybean, pea, and Athila-like elements of Arabidopsis. A new consensus sequence was determined from the coding regions of the protease, reverse transcriptase, and integrase (pages 56-57, Example 4). A summary of the sequence listing on pages 19-20 indicates that SEQ ID NO: 1 and 2 are specialized primer binding site version 1 and 2, respectively, and that SEQ ID NO: 9 encodes SEQ ID NO: 10 which is generic integrase; SEQ ID NO: 11 encodes SEQ ID NO: 12 which is generic reverse transcriptase; SEQ ID NO: 15 encodes SEQ ID NO: 16 which is generic RNAseH; SEQ ID NO: 5 encodes SEQ ID NO: 6 which is generic envelope; and SEQ ID NO: 3 and 4 are specialized polypurine tract and targeting sequence, respectively.

However, nucleotide sequences of the instant claims encompass any nucleotide sequences that are at least about 95% identical to SEQ ID NO: 2 or nucleotide sequences that are at least about 70% identical to SEQ ID NO: 9, or nucleotide sequences encoding polypeptides having at least 75% identity to SEQ ID NO: 10 or nucleotide sequences that are at least about 70% identical to SEQ ID NO: 11, or nucleotide sequences encoding polypeptides having at least 79% identity to SEQ ID NO: 12, or nucleotide sequences that are at least about 70% identical to SEQ ID NO:

15, or nucleotide sequences encoding polypeptides having at least 90% identity to SEQ ID NO: 16, or nucleotide sequences that are at least about 50% identical to SEQ ID NO: 5, or nucleotide sequences encoding polypeptides having at least 30% identity to SEQ ID NO: 6. Although, as discussed above, the specification use bioinformatics software to generate those generic protein/nucleotide sequences as indicated by SEQ ID NO: 5,6,9-12,15 and 16, they are obtained only by the sequence alignment without any experimental verification. There is no indication about the function importance of these motifs. Falcon-Perez JM et al. (1999, *J Biol Chem.* 274:23584-90) teach that when twenty-two single amino acid substitutions or deletions were introduced into the nucleotide binding domains, the proposed regulatory domain, and the fourth cytoplasmic loop of the yeast cadmium factor (Ycf1p) vacuolar protein by site-directed mutagenesis, two conserved amino acid residues, Glu (709) and Asp (821), were found to be unnecessary for Ycf1p biogenesis and function. The instant specification fails to provide guidance for which amino acids of SEQ ID NO: 14 can be altered, the type of alteration, and which amino acids must not be changed, to maintain DGAT activity of the encoded protein. The specification also fails to provide guidance for which amino acids can be deleted and which regions of the protein can tolerate insertions and still produce a functional enzyme.

Making "conservative" substitutions (*e.g.*, substituting one polar amino acid for another, or one acidic one for another) does not produce predictable results. Lazar et al. (1988, Mol. Cell. Biol. 8:1247-1252) teach that the "conservative" substitution of glutamic acid for aspartic acid at position 47 reduced biological function of transforming

growth factor alpha while "nonconservative" substitutions with alanine or asparagine had no effect (abstract). Similarly, Hill et al (1998, Biochem. Biophys. Res. Comm. 244:573-577) teach that when three histidines that are maintained in ADP-glucose pyrophosphorylase across several species are substituted with the "nonconservative" amino acid glutamine, there is little effect on enzyme activity, while the substitution of one of those histidines with the "conservative" amino acid arginine drastically reduced enzyme activity (see Table 1). All these mutated proteins would have at least 95% identity to the original protein.

Guo et al. (2004, Proc. Natl. Acad. Sci. USA 101: 9205-9210) teach that while proteins are fairly tolerant to mutations resulting in single amino acid changes, increasing the number of substitutions additively increases the probability that the protein will be inactivated (pg 9209, right column, paragraph 2). Thus, making and analyzing claimed nucleic acid sequences or proteins would require undue experimentation.

Further more, the polypeptide of SEQ ID NO: 6 encoded by SEQ ID NO: 5 may not be envelope protein as indicated in the table on page19-20 according to Chavanne et al. who teach a Cyclops form pea which has the same overall structure and sequence homology to claimed Calypso retrovirus-like elements from soybean (page 53, line 20-21). Chavanne et al. (1998, *Plant Mol.* Biol. 37:363-375) teach that it is possible an additional 3'ORF of 423 codons represents an unknown gene of legume host cell which have been captured and amplified by Cyclops during transposition (page 373, 2$^{nd}$ paragraph of left column). Chavanne et al. further teach that genes encoding ENV

functions are very heterogeneous at the sequence level and difficult t identify by homology even between retroviruses (page 373, 2nd paragraph of left column). In any case, functions of the protein of SEQ ID NO: 6 need to be verified experimentally in the future. The structure required for such unknown function can only be determined after the function of the protein is identified.

Given claim breadth, unpredictability of the art, and lack of guidance as discussed above, undue experimentation would have been required by one skilled in the art to develop and evaluate nucleotide sequences that are at least about 95% identical to SEQ ID NO: 2 or nucleotide sequences that are at least about 70% identical to SEQ ID NO: 9, or nucleotide sequences encoding polypeptides having at least 75% identity to SEQ ID NO: 10 or nucleotide sequences that are at least about 70% identical to SEQ ID NO: 11, or nucleotide sequences encoding polypeptides having at least 79% identity to SEQ ID NO: 12, or nucleotide sequences that are at least about 70% identical to SEQ ID NO: 15, or nucleotide sequences encoding polypeptides having at least 90% identity to SEQ ID NO: 16, or nucleotide sequences that are at least about 50% identical to SEQ ID NO: 5, or nucleotide sequences encoding polypeptides having at least 30% identity to SEQ ID NO: 6, and that still maintain their functions.

Furthermore, it is well known that the pol region contains sequence motifs related to enzymes protease, reverse transcriptase, RNAseH and integrase in the same typical order (5'-PR-RT-RH-IN-3') (Chavanne et al. abstract). The claimed nucleotide sequence, however, contains a different order without support from either the specification or the prior art. The support is also not found for a retrovirus-like element

having both SEQ ID NO: 1 and 2, which results in two copies of PBS. Neither the specification nor the prior teaches two copies of PBS in the retro-element. Undue experimentation would be required to test if such modification could affect the function of the element.

Still further, the claimed nucleotide sequences do not include explicitly or implicitly gag protein, polypurine tract, protease, and LTR regions as shown by Chavanne et al. (1998, *Plant Mol.* Biol. 37:363-375, Figure 1). It is unclear how a person skilled in the art is able to use such claimed nucleotide sequences missing those essential elements. The specification does not teach how the claimed retro-element can be used for genetic engineering of plants. Peterson-Burch et al. (2000, *Trends in Genetics* 16:151-152) teach that while disarmed, non-infectious animal retroviruses are used as vectors for gene transfer, it is important to first understand how plant retroviruses naturally contribute to interspecies gene flow before they can be used as vectors for plants as well (page 152).

See *Genentech Inc. v. Novo Nordisk,* A/S (CA FC)42 USPQ2d 1001 (Fed. Cir. 1997), which teaches that "the specification, not the knowledge of one skilled in the art" must supply the enabling aspects of the invention.

Given the discussion above, undue experimentation would be required for a person skilled in the art to use the claimed nucleotide sequence.

***Conclusion***

Claim 49 is rejected. The claim, however, is deemed free of prior art due to the failure of the prior art to teach or fairly suggest the claimed nucleotide sequence.

Please note that an obviousness-type double patenting rejection is not made over claim 1 of U.S. Patent No. 6,331,662 due to that SEQ ID NO: 17 in patented claim does not anticipate two PBS elements (SEQ ID NO: 1 and 2).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Li Zheng whose telephone number is 571-272-8031. The examiner can normally be reached on Monday through Friday 9:00 AM - 6:30 PM EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anne Marie Grunberg can be reached on 571-272-0975. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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